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(54) Title: PROCESS FOR THE PREPARATION OF REPAGLINIDE

(57) Abstract: The present invention relates to a cost effective and industrially advantageous process for the preparation of repaglinide.



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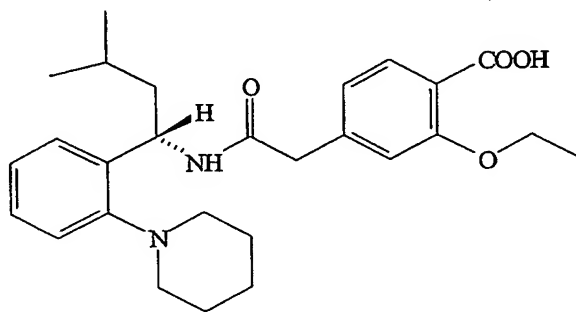
PROCESS FOR THE PREPARATION OF REPAGLINIDE

Field of the Invention

The present invention relates to a cost effective and industrially advantageous process for the preparation of repaglinide.

Background of the Invention

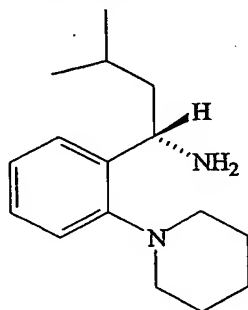
Chemically, repaglinide is S(+)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}aminocarbonylmethyl]benzoic acid having the Formula I,



FORMULA I

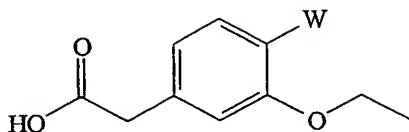
and is known from U.S. Patent No. 5,312,924. It belongs to a new class of hypoglycemic benzoic acid derivatives. It offers significantly better biological profile as compared to sulphonylurea class of compounds for the treatment of non-insulin dependent diabetes mellitus (NIDDM).

U.S. Patent No. 5,312,924 describes a process for the preparation of repaglinide which involves the reaction of (S)-amine of Formula II,



FORMULA II

with a carboxylic acid of Formula III,



5

FORMULA III

wherein W represents a (protected) carboxy group or a reactive derivative thereof, and cleaving the protecting group, if necessary, to obtain repaglinide of Formula I.

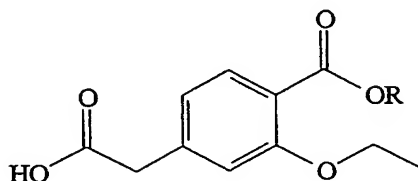
The reaction of the (S)- amine of Formula II with a carboxylic acid of Formula III is carried out in the presence of N, N'-carbonyldimidazole, N, N'-dicyclohexylcarbodiimide or triphenylphosphine/carbon tetrachloride and triethylamine. N,N'-carbonyldimidazole is expensive and gives low yields (50 to 55%) while the use of triphenylphosphine/carbon tetrachloride necessitates chromatographic purification to obtain repaglinide of desired purity. The use of N, N'-dicyclohexylcarbodiimide generates dicyclohexyl urea as a by-product which can only be removed by repeated crystallizations of the product resulting in increased cycle time and the cost of production. Furthermore, the N, N'-dicyclohexylcarbodiimide is toxic and its use on a commercial scale is undersirable.

Several variations of this method are known which involve the condensation of differently substituted amines and carboxylic acids, followed by suitable chemical modification of the substituents to obtain repaglinide. All of these variations involve additional number of synthetic steps and are therefore not suitable for commercial scale production of repaglinide.

It is, therefore desirable to solve the problems associated with the prior art and to provide an efficient process for the preparation of repaglinide which process improves the economics by employing less expensive and less hazardous raw materials and is more productive. The process avoids the tedious and cumbersome procedures of chromatography or special recrystallization techniques, is economical and convenient to operate on a commercial scale.

The present invention provides a process for the preparation of repaglinide of Formula I comprising :

a) reacting the (S)- amine of Formula II with a protected carboxylic acid of Formula IV,



FORMULA IV

10 wherein R is a protecting group, in the presence of pivaloyl chloride and a base, and

b) removing the protecting group to obtain repaglinide.

The protecting group R in the compound of Formula IV is any carboxylic acid protecting group which is easily removed, such as methyl, ethyl, tert.-butyl, benzyl, p-nitrobenzyl, p-methoxybenzyl, and the like.

15 The reaction is carried out in the presence of a suitable base which may be either organic or inorganic. Examples of suitable organic bases include amines such as diisopropylamine, dicyclohexylamine, 1,8-diazabicyclo[5.4.0] undec-7-ene, triethylamine, tributylamine, N, N-dimethylaniline, diisopropylethylamine, and the like. Suitable inorganic bases include potassium carbonate, sodium carbonate, and the like.

20 The reaction may be carried out in a suitable solvent such as dichloromethane, toluene, xylene, and the like. The reaction is carried out at temperatures of between -25°C and 40°C, but preferably at temperatures of between -10 and 25°C.

The removal of a carboxylic acid protecting group is achieved by suitable methods known in the art such as acidic or basic hydrolysis or hydrogenolysis.

Detailed Description of the Invention

In the following section one preferred embodiment has been described by way of example to illustrate the process of the invention. However, it is not intended in any way to limit the scope of the present invention.

EXAMPLE

Preparation of ethyl (S)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl} aminocarbonylmethyl]benzoate

Pivaloyl chloride (5.4g, 45 mmol) was added to a mixture of 3-ethoxy-4-ethoxycarbonyl phenylacetic acid (10.0g, 40 mmol), toluene (50ml) and triethylamine (5.0g, 49 mmol) at -5°C and stirred for 1 hour. A solution of (S)-3-methyl-1-(2-piperidinophenyl)-1-butylamine (9.8g, 40 mmol) in toluene (20ml) was then added at below 10°C. The temperature of the reaction mixture was raised to 30°C and the mixture stirred overnight. It was then washed with water and saturated sodium bicarbonate solution. Toluene was distilled off under reduced pressure to get the crude product. The crude product was dissolved in toluene (35ml), hexane (200ml) was added and the mixture cooled at 0°C. The solid product so obtained was filtered and dried to give 14.0g of the title compound (Yield: 73%, HPLC Purity 99%).

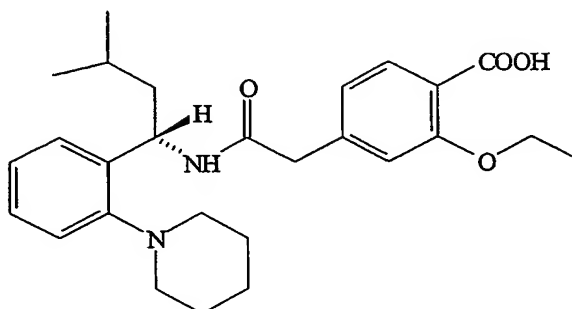
Preparation of (S)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl} aminocarbonylmethyl]benzoic acid

A solution of ethyl (S)-2-ethoxy-4-[N-{1-(2-piperidinophenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]benzoate (20g, 41.6 mmol) in denatured spirit (200ml) was stirred at 60-65°C and 1N sodium hydroxide solution (62ml) was added. After two hours of stirring at 60°C, the reaction mixture was cooled to 35°C and pH was adjusted to about 5.0 using 1N hydrochloric acid (about 70ml). The solution was stirred for 30 minutes at 35-40°C, cooled to 0°C and stirred at 0 to 5°C for one hour to get a crystalline product. The crystals were separated by filtration and washed with water. The product was dried at 60-65°C under vacuum to get repaglinide (17.8g, Yield : 94%, Assay 99.5% by HPLC).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

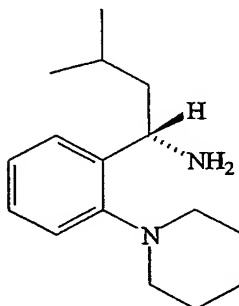
CLAIMS :

1. A process for the preparation of repaglinide of Formula I,

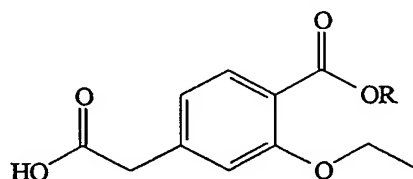
**FORMULA I**

comprising :

- a) reacting the (S)- amine of Formula II,

**FORMULA II**

15 with a protected carboxylic acid of Formula IV,

**FORMULA IV**

20 wherein R is a protecting group, in the presence of pivaloyl chloride and a base,
and

b) removing the protecting group to obtain repaglinide.

2. The process according to claim 1 wherein the protecting group R is selected from the group consisting of methyl, ethyl, tert.-butyl, benzyl, p-nitrobenzyl, and p-methoxybenzyl.
- 5 3. The process according to claim 1 wherein the reaction is carried out in the presence of an organic or inorganic base.
4. The process according to claim 3 wherein the organic base is an amine.
5. The process according to claim 4 wherein the amine is selected from the group consisting of 1,8-diazabicyclo[5.4.0]undec-7-ene, triethylamine, tributylamine, N,
10 N-dimethylaniline, diisopropylethylamine diisopropylamine, and discyclohexylamine.
6. The process according to claim 3 wherein the inorganic base is potassium carbonate or sodium carbonate.
7. The process according to claim 1 wherein the reaction is carried out in a solvent.
- 15 8. The process according to claim 7 where the solvent is selected from the group consisting of dichloromethane, toluene and xylene.
9. The process according to claim 1 wherein the reaction is carried out temperatures of between -25°C and 40°C .
10. The process according to claim 9 wherein the temperature is -10° to 25°C .

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB 02/03943

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/32 A61K31/445 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 312 924 A (SAUTER ROBERT ET AL) 17 May 1994 (1994-05-17) cited in the application page 33 -page 34; example 11 ---	1
A	GRELL W ET AL: "REPAGLINIDE AND RELATED HYPOGLYCEMIC BENZOIC ACID DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, 1998, pages 5219-5246, XP000872800 ISSN: 0022-2623 scheme 2. and scheme 3. --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

10 February 2003

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/IB 02/03943

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>GUAY D R P: "REPAGLINIDE, A NOVEL, SHORT-ACTING HYPOGLYCEMIC AGENT FOR TYPE 2 DIABETES MELLITUS" PHARMACOTHERAPY, BOSTON, US, vol. 18, no. 6, 1998, pages 1195-1204, XP000874581 ISSN: 0277-0008 the whole document</p>	1
A	<p>PATENT ABSTRACTS OF JAPAN vol. 008, no. 168 (C-236), 3 August 1984 (1984-08-03) & JP 59 065094 A (SUMITOMO KAGAKU KOGYO KK), 13 April 1984 (1984-04-13) abstract</p>	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal application No
PCT/IB 02/03943

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